ICH

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Q1D

Bracketing and matrixing designs for stability testing of drug substances and drug products

Step 2 9 November 2000

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INTRODUCTION

1.1 Objectives of the Guideline

The objective of this guideline is to provide harmonised guidance on the application of bracketing and matrixing for stability studies conducted in accordance with principles outlined in the ICH Q1A Harmonised Tripartite guideline covering Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

1.2 Background

Q1A notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products, but provides no further guidance on the subject.

1.3 Scope of the guideline

This document is an annex to the parent guideline and addresses recommendations for bracketing and matrixing study designs. Specific principles are provided in this guideline for situations in which bracketing or matrixing can be applied without further justification. In other circumstances, bracketing or matrixing is applicable only if further justification is provided. Sample designs are provided in this guideline for illustrative purposes, and should not be considered the only, or the most appropriate, designs in all cases.

2 GUIDELINES

2.1 General

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design, is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved in the drug substance or product being evaluated. Any reduced design should retain the ability to adequately detect differences in stability resulting from any of the design factors. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter shelf life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, if it becomes apparent that the reduced testing is no longer appropriate because, for example, the product appears less stable than expected, a modified design, that either reverts to full testing or to a less reduced testing design, can be followed. Once the design is reverted, full testing or less reduced testing should be carried out through the proposed retest period or shelf life.

2.2 Applicability of Reduced Designs

Reduced designs can be applied to the stability study of most types of drug products, when appropriate. For the study of drug substances, matrixing is of limited utility and bracketing is generally not applicable.

Bracketing or matrixing can be applied with or without justification depending on the circumstances as discussed in detail below. The degree of justification in each of these cases will depend on the available supporting data on the product. Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied.

Bracketing and matrixing are reduced designs based on different principles. Therefore, the use of bracketing and matrixing together in one design should be considered and scientifically justified.

Reduced designs can be used for formal stability studies if the principles outlined below are followed.

2.3 Bracketing

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes of or different fills in the same container closure system.

The use of a bracketing design would not be appropriate if it cannot be demonstrated that the strengths or container sizes and fills selected for testing are indeed the extremes.

2.3.1 Design Factors

Design factors are variables (e.g. strength, container size, fill) to be evaluated in a stability design for their effect on product stability.

2.3.1.1 Strength

Bracketing can be applied without further justification to studies with strengths of identical or closely related formulations. Examples include capsules of different strength made with different fill plug sizes from the same powder blend, tablets of different strengths manufactured by compressing varying amounts of the same granulation, and formulations that differ only in minor excipients, e.g., colorants, flavourings.

Bracketing can be applied with justification where the relative amounts of drug substance and excipients change in a formulation. For cases where different excipients are used amongst strengths, generally bracketing should not be applied.

2.3.1.2 Container Closure Sizes and Fills

Bracketing can be applied without further justification to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes of packaging configurations by comparing the various characteristics of the container closure system that may affect the product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, head space to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.

Bracketing can be applied with justification in studies for the same container when the closures vary. Justification could include a discussion of the relative permeation rates of the bracketed container closure system.

2.3.2 Design Considerations and Potential Risks

If, after starting the studies, one of the extremes is no longer expected to be marketed, the study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes.

Before a bracketing design is applied, its effect on retest period or shelf life estimation should be assessed. If the stability of the extremes is shown to be different, the intermediates should be considered to be no more stable than the least stable extreme, i.e., the shelf life for the intermediates should not exceed that for the least stable extreme.

2.3.3 Design Example

A typical bracketing example is given in Table 1. This example is based on a product available in three strengths and three container sizes. In this instance it should be demonstrated that the 15 ml and 500 ml HDPE container sizes bracket the 100 ml size. The batches for each selected combination should be tested at each time point as in a full design.

Table 1. Example of a Bracketing Design

Strength		50mg			75mg			100mg		
Batch		B1	B2	B3	B4	B5	B6	B7	B8	B9
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: B1-B9 indicate batches T = sample tested

2.4 Matrixing

As defined in the glossary to the parent guideline, matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied, if justified, with different testing frequencies.

2.4.1 Design Factors

Matrix designs can be applied without further justification to strengths with identical or closely related formulations. Examples include capsules of different strength made with different fill plug sizes from the same powder blend, tablets of different strengths manufactured by compressing varying amounts of the same granulation, and formulations that differ only in minor excipients, e.g., colorants or flavourings.

Other examples of design factors that can be matrixed without further justification include: batches made using the same process and equipment; container size and fill in the same container closure system.

Matrix designs can be applied with justification to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used, or to different container closure systems. Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapour transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light.

2.4.2 Design Considerations

A matrix design should be balanced such that each combination of factors is tested to the same extent over the intended duration of the study and, as far as possible, at the intended submission time.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain fractions of the designated combinations should be tested at each intermediate time point. If full long-term data for the proposed shelf life will not be available for review before approval, all selected combinations of batch, strength, container size and fill, etc., should also be tested at 12 months or at the last time point prior to submission. In addition, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study. For matrixing at an accelerated or intermediate storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

When a matrix on design factors is applied, if one strength or container size fill is no longer intended for marketing, stability testing of that strength or container size fill can be continued in order to support the other strengths or container sizes and fills in the design.

2.4.3 Example Designs

2.4.3.1 Simple Designs

Examples of simple designs for a product in two strengths (S1 and S2) are shown in Table 2. The term *one half reduction, one third reduction,* etc., refers to the reduction strategy initially applied to the full study design. For example, a one half reduction initially eliminates one in every two time points from the full study design and a one third reduction initially removes one in every three. In the examples shown in Table 2, the reductions are less than one half and one third due to the inclusion of full testing of all factor combinations at some time points as discussed in section 2.4.2. These examples include full testing at the initial, final and at the twelve month time points. The ultimate reduction is therefore less than one half (24/48) or one third (16/48), and is actually 15/48 or 10/48, respectively.

Table 2 Example matrix designs on time points for a product with two strengths

One Half reduction

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

T = Sample tested

One Third reduction

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

T = Sample tested

2.4.3.2 Complex Designs

Matrix designs can be either complete, where all combinations of factors are tested, or incomplete, where some combinations are not tested at all. An example of a more complex matrix using a one third reduction design with full testing at 12 months is given in Tables 3a and 3b. Table 3a shows a complete design, and Table 3b an incomplete design. In Table 3b, while all combinations of strength and container size are tested, each individual batch of product is not tested in all strength and container size combinations.

Tables 3a and 3b: Examples of complete and incomplete matrix designs for a product with 3 strengths and 3 container sizes

3a Complete Design

Strength	S1				S2				S3		
Container size	A	B	C		A	B	C		A	B	C
Batch 1	T1	T2	T3		T2	T3	T1		T3	T1	T2
Batch 2	T2	T3	T1		T3	T1	T2		T1	T2	T3
Batch 3	T3	T1	T2		T1	T2	T3		T2	T3	T1

3b Incomplete design

Strength	S1				S2				S3		
Container size	A	B	C		A	B	C		A	B	C
Batch 1	T1	T2			T2		T1			T1	T2
Batch 2		T3	T1		T3	T1			T1		T3
Batch 3	T3	T1	T2			T2	T3		T2	T3	

Key:

Time point (months)	0	3	6	9	12	18	24	36
T1	T		T	T	T	T	T	T
T2	T	T		T	T		T	T
T3	T	T	T		T	T		T

S1, S2 and S3 are different strengths. A,B and C are different container sizes
T = Sample tested

2.4.4 Applicability and Degree of Reduction

In choosing a matrix design, knowledge of data variability, the expected stability of the product, the availability of supporting data, any stability differences in the product within a factor or among factors, and/or number of factor combinations in the matrix should be considered.

In general, a matrix design is applicable if the supporting data indicate very small variability and excellent product stability. Where the supporting data exhibit moderate variability and moderate product stability, a matrix design should be statistically justified. If the supportive data show large variability and poor product stability, a matrix design should not be applied.

A statistical justification could be based on an evaluation of the proposed matrix design with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.

If a matrix design is considered applicable, the degree of reduction that can be made from a full design is dependent upon the number of factor combinations being evaluated. The more factors associated with a product and the more levels in each factor, the larger the degree of reduction that can be considered.

Any matrix design should retain an adequate ability to detect stability differences within factors or among factors.

2.4.5 Potential Risk for Matrix Design

Due to the reduced amount of data collected, a matrix design on factors other than time point generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may not have sufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation.

If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations. A complete design that matrixes on time points only would often have similar ability to that of a full design to detect differences in rates of change among factors and to establish a reliable retest period or shelf life. This feature exists because linearity is assumed, and because full testing of all factor combinations would still be performed at both the initial time point and the last time point prior to submission.

2.5 Data evaluation

Stability data from studies in a reduced design should be treated in the same manner as data from full design studies as described in the parent guideline.